Association of seventeen definitions of remission with functional status in a large clinical practice cohort of patients with rheumatoid arthritis

METEOR registry

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Abstract

Objective: To compare the association between different remission criteria and physical function in rheumatoid arthritis patients followed in clinical practice.

Methods: Longitudinal data from the METEOR database were used. Seventeen definitions of remission were tested: ACR/EULAR Boolean-based; Simplified/Clinical Disease Activity Index (SDAI/CDAI); and fourteen Disease Activity Score (DAS)-based definitions. Health Assessment Questionnaire (HAQ)≤0.5 was defined as good functional status. Associations were investigated using generalised estimating equations (GEE). Potential confounders were tested and sensitivity analyses performed.

Results: Data from 32,915 patients (157,899 visits) were available. The most stringent definition of remission was the ACR/EULAR Boolean-based definition (1.9%). The proportion of patients with HAQ≤0.5 was higher for the most stringent definitions, although it never reached 100%. However, this also meant that, for the most stringent criteria, many patients in non-remission had HAQ≤0.5. All remission definitions were associated with better function, with the strongest degree of association observed for the SDAI (adjusted OR (95% CI): 3.36 (3.01-3.74)). However, only minor differences were noted between definitions (range of adjusted OR 1.99 to 3.36). Sensitivity analyses yield similar results.

Conclusions: The seventeen definitions of remission confirmed their validity against physical function in a large international clinical practice setting. Achievement of remission, according to any of the indices may be more important than the use of a specific index. A multidimensional approach, targeted at wider goals than disease control, is necessary to help all patients achieve the best possible functional status.

Background

Significant advances in the management of rheumatoid arthritis (RA) have taken place in the last decades, allowing the establishment of remission as the target of treatment in clinical trials, and in routine clinical practice.(1, 2)

In spite of the existing agreement concerning the importance of achieving remission in order to prevent joint destruction and functional disability, there is still no consensus regarding the definition of such goal. Ideally, remission should represent the absence or a very low state of disease activity, and should be validated against long-term outcomes, such as physical function and radiographic progression. The stringency of such a threshold will obviously influence the percentage of patients who reach it.(2-7)

Several definitions of remission have been proposed, including the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition and others based on composite indices such as the Disease Activity Score (DAS), with multiple variations and proposed cut-offs, the Clinical Disease Activity index (CDAI) and the Simplified Disease Activity Index (SDAI).(1, 2, 7)

A total of seventeen definitions of remission in RA can be found in the literature, all of them validated to some extent. These definitions refer to the ACR/EULAR, CDAI, SDAI and those definitions based on DAS and DAS28 [each one encompassing information on C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and considering or not considering patient global assessment]. (8-15) In addition, multiple DAS28 cut-offs have been proposed, making a total of 17 definitions using different formulae and cut-offs. However, in previous studies the number of definitions compared, patient numbers, or duration of follow-up were limited and few reports related remission to functional status. Moreover, most previous studies come from single centres or culturally homogeneous groups and none directly compared the full list of definitions, some of which were published in the last year (e.g. newly proposed 28-joint count DAS (DAS28) cut-offs).(14, 15)

The aim of the present study was to compare the prevalence of remission according to various criteria and to study the relationship between remission and physical function in a large multinational cohort of real-life patients with RA.

Methods

For this study, longitudinal data from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database were used. METEOR is a software tool, designed by and for rheumatologists, available online for free, which allows longitudinal registration of disease activity and disability measures. Data can either be entered directly on the online tool or uploaded from local electronic health record systems or registries. Details of the METEOR tool have been previously described.(16-18) The database used in this work included visits from June 1985 till November 2015.

Seventeen definitions of remission were tested: the ACR/EULAR Boolean-based definition of remission (tender joint count≤1, swollen joint count≤1, C-reactive protein ≤1 mg/dl and Patient Global Assessment (PGA) ≤1 (on a 0–10 scale)), SDAI ≤3.3, CDAI ≤2.8 and the fourteen definitions based on DAS (which includes the Ritchie articular index and a 44-swollen joint count) and DAS28 (which includes a 28-swollen and -tender joint count), taking into account various proposed formula (with CRP/ESR, with/without PGA) and the various cut-offs proposed for the same formula. Those definitions were the DAS score <1.6 (definition with ESR or CRP), DAS28 score <2.6 (definition with ESR or CRP), always dichotomizing for patient global assessment (ie, 3 or 4 variables). In addition, newly suggested DAS28 cut-offs were also considered: DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].(14, 15) Disability was measured by the Health Assessment Questionnaire (HAQ) and HAQ≤0.5 defined as "good functional status".(19)

Associations were investigated through generalised estimating equations (GEE), using HAQ≤0.5 as the dependent variable and the various remission criteria as independent variables. GEE allow the combination of multiple measurements per patient, use all available data during follow-up, while taking into account missing values and correcting for within-patient correlation.(20) With GEE, each visit counts as an independent assessment and is used to classify the remission status of the patient, which may change over time. However, GEE allows the use of all longitudinal data because it takes the dependency of observations (within subject/patient-correlation) into account. Models were adjusted for potential confounders, namely treatment with biological disease-modifying antirheumatic drugs (bDMARDs), body mass index (BMI), age, gender, smoking status, Gross National Income per capita, disease duration, anti-citrullinated peptide antibody (ACPA) status, rheumatoid factor (RF) status, and presence of erosions. Both age and BMA were dichotomised using the median value. Sensitivity analyses were performed using sets of data limited to first visits only and to patients with no missing data for all definitions of remission. A flow chart representing the number of patients and visits taken into consideration in the various sub-analyses is presented in figure 1. The METEOR registry contains completely anonymised data which was gathered during daily practice. There is no link between the anonymised data and the

original patient identity, according to current General Data Protection Regulation. Treatment, timing of follow-up visits and measurements were non-protocolled. Therefore medical ethics board approval was not required.

Results

Study population

Data from 32,915 patients and 157,899 visits were available [average 6.9 (SD 7.9) visits/per patient]. The socio-demographic and clinical characteristics at the first visit are described in Table 1, for all patients al for those with information about all definitions of remission (n=9,902). Regarding treatments, 42.2% were receiving corticosteroids, 72.8% csDMARDs and 11.1% bDMARDs. The mean HAQ was 1.0 (0.8) (table 1).

Data were not available for all patients; the number of patients with valid information for each variable at the first visit is presented in table 1.

The study population resulting from this international initiative assembled patients from different countries as presented in supplementary table 1.

Fulfilment of the definitions of remission

The most stringent definitions of remission, as observed in the first METEOR visit, were the ACR/EULAR Boolean-based definition (1.9%) and the SDAI≤3.3 (6.1%). Regarding the various remission criteria based on the DAS, the percentages of first visits in remission ranged between 6.5 (for the newly proposed DAS28-CRP-3v cut-off of 1.9) and 20.4% (for the DAS-ESR-4v cut-off of 1.6) (table 2).

Remission data taking all visits into account are also presented in table 2. As expected, the percentage of visits with patients in remission increased at follow-up. The most stringent definitions of remission in this analysis were the ACR/EULAR Boolean-based definition (4.5%) and the CDAI (13.4%). The percentage of visits in SDAI remission was 17.1%, and regarding the various remission criteria based on the DAS, the percentages of visits with patients achieving remission ranged between 15.2% (for the newly proposed DAS28-ESR-3v cut-off of 2.2) and 39.1% (for the DAS-CRP-3v cut-off of 1.6).

Remission data regarding the subset of visits with information on all definitions of remission are presented in supplementary table 2. Results for this subset of patients were very similar to those described above.

<u>Proportion of visits with patients with good functional status among visits with and without disease activity remission status</u>

As presented in table 3, at first visit, the proportion of visits with HAQ≤0.5 among patients in remission was higher for the most stringent definitions (88.8% for ACR/EULAR Boolean-based, 81.7% for SDAI, 80.5% for CDAI). A significant proportion of visits with patients in non-remission had HAQ≤0.5 (e.g. 29.3% for ACR/EULAR Boolean-based definition, 21.6% of patients without SDAI remission, and 25.1% of patients without CDAI remission). The prevalence of good functional status in visits with patients fulfilling DAS/DAS28 remission definitions ranged from 54.5% (for DAS-CRP-3v<1.6) to 75.3% (for DAS28-CRP-4v<1.9). Among visits with patients not fulfilling DAS/DAS28 remission, the proportion of patients with good functional status ranged from 20.1% (for patients not fulfilling DAS28-CRP-4v<2.6) to 30.1% (for patients not fulfilling DAS28-ESR-3v<2.2). Very similar results were obtained when all visits in the database were considered (table 3) and when only patients with information available for all definitions of remission were considered (supplementary table 3).

In summary, a significant proportion of patients in remission reported HAQ scores>0.5 at the same visit (11.2 to 45.5%) and a significant proportion of patients in non-remission had HAQ scores≤0.5 (19.3 to 34.1%). The proportion of patients in non-remission that had HAQ≤0.5 was higher for the most stringent definitions (table 3).

<u>Associations between remission and good functional status</u>

The strongest association between remission and good functional state was observed for the SDAI definition of remission [odds ratio (OR) = 3.774, confidence interval (CI) = (3.492, 4.078)]. However, results did not differ significantly between definitions of remission (table 4), with the majority of 95% CI for the OR overlapping. Similar results were obtained when the model was adjusted for significant cofactors [SDAI adjusted OR = 3.357, CI = (3.012, 3.742)]. Remission criteria based on DAS were more strongly associated with good functional status when 4v definitions were used (OR_{4v} between 2.778 and 3.365) compared to when 3v definitions were considered (OR_{3v} between 2.204 and 2.809). When CI of similar scores were compared, the lower limit of the OR for the 4v definition was always higher than the higher limit of the comparable 3v

definition. A similar tendency was observed when adjusted ORs were compared, however some overlapping CI were observed.

When analysing only visits with information available for all definitions of remission, (Table 5) the SDAI definition of remission remained the most strongly associated with good functional status [OR = 3.629, CI = (3.338, 3.945)]. Once again, DAS-based remission criteria presented a trend to be more associated with good functional status when 4v models were considered (OR_{4v} between 2.769 and 3.406), in comparison to 3v models (OR_{3v} between 2.248 and 3.016). However, overlaps between CI were observed for some definitions. In this analysis, when ORs were adjusted for significant cofactors, the strongest association between remission and good functional status was observed for DAS-CRP-4v <1.6 [OR = 3.793, CI = (3.354-4.289)], followed by SDAI [OR = 3.549, CI = (3.107-4.053)] (table 4).

Stringency of the newly proposed DAS28 remission cut-offs

As expected, the new cut-offs for DAS28 remission (DAS28-CRP<1.9 and DAS28-ESR<2.2) were associated with a lower percentage of visits in remission (range between 6.5% and 9.9% vs. 14.9% and 16.3%, respectively, at first visit – table 2). However, they were still less stringent than the ACR/EULAR Boolean-based or SDAI criteria (1.9% and 6.1%, respectively). Similar results were obtained when all visits were taken into account (table 2). Their degree of association with good functional status (OR between 2.2 and 3.2) was similar to the older cut-offs (OR between 2.4 and 3.4).

Discussion

This study confirmed the correspondence between various remission definitions and physical function in a large international clinical practice setting. We found that the most stringent definition of remission was the ACR/EULAR Boolean-based definition and confirmed that the newly proposed DAS28 remission cut-offs (DAS28-CRP<1.9 and DAS28-ESR<2.2) result in remission rates that are closer to the most stringent definitions. The proportion of patients with good functional status among patients in remission was higher for the most stringent definitions. However, being in clinical remission was not always equivalent to having good functional status. Conversely, some patients in non-remission had good functional status. The proportion of patients with good functional status among patients in non-remission was notoriously higher when the most stringent definitions of remission were used.

The strongest degree of association between remission and good functional status was observed for the SDAI. However, differences between the various definitions were generally minor. Results were highly consistent in all the analyses performed, namely using first visits only, all visits or only visits with complete data for all the seventeen definitions of remission.

ACR/EULAR, CDAI and SDAI remission criteria had already been previously described as the most stringent definitions of remission. In a German database with 6,864 RA patients, the percentages of remission according to DAS28-ESR-4v<2.6, SDAI and ACR/EULAR Boolean-based definitions were 28.1%, 10.8%, and 6.9%, respectively.[21] CDAI criteria were not evaluated in this study. We found that CDAI remission criteria were more stringent than SDAI (when all visits were taken into account). In a paradigmatic clinical trial (the BeSt study), in which 508 RA patients with early disease were included, ACR/EULAR, CDAI and SDAI remission criteria also classified a lower proportion of patients as being in remission compared to the indices based on DAS28. This study also demonstrated a positive association between remission and good functional status defined by a HAQ≤0.5.[12]

A higher proportion of patients in good functional status was observed for the most stringent definitions (ACR/EULAR Boolean-based, SDAI ≤3.3 and CDAI ≤2.8). A tendency to a stronger association between remission and good functional status was observed for the SDAI definition. The ORs obtained with different definitions were very similar and confidence intervals overlapped. Remission criteria based on DAS presented a trend to be a stronger predictor of good functional status when the 4v definitions were used. This was confirmed by sensitive analyses, and probably reflects the impact of functional status upon the PGA score, included in the 4v definitions. This is in line with the observation by Ferreira et al[22] that PGA in patients with RA is strongly associated with disease impact factors, such as function, fatigue, pain and anxiety, and only weakly with

disease activity. This is even more pronounced in patients who keep high PGA scores in the absence of overt signs of inflammation.

As mentioned above, despite the clear association between the two, remission does not always mean good functional status. Some recent studies suggest that coping strategies may contribute to the dissociation between remission and good functional status observed in a sizeable proportion of patients. Patients with effective coping tend to report a less severe functional impairment in RA(23) and in other rheumatic diseases.(24)

The new remission definitions for DAS28(14) confirmed in this setting a tendency to have a stronger association with good functional status than the previous ones. This may suggest that these definitions should be preferable. However, the argument is complex: when Thiele et al compared RA patients to a randomly matched sample from the general German population, they found that patients fulfilling DAS28-ESR-4v remission criteria had a functional status that was identical to the matched controls, but those who fulfilled SDAI or Boolean-based remission criteria had a considerably better functional status than the matched controls.(21) This suggests that the new Boolean-based and SDAI criteria may select super-normal patients that are not only free from active RA but also from other comorbid conditions and have the most effective coping strategies. As activity indices are used to guide clinical treatment decisions, it is very important that clinicians are aware of this issue, in order to avoid overtreatment.(25) Patients with comorbid conditions, including other musculoskeletal conditions such as osteoarthritis and fibromyalgia, may never be able to meet the most stringent remission criteria, even if RA is brought under absolute control and has no functional impact of its own.(26) Patients with comorbidities, who represent the norm in clinical practice, will benefit more from guided treatments to the specific comorbidity, than from immunosuppressive agents.

Our study included data from 32,915 patients and 157,899 visits from all around the world. This makes it the largest study ever performed addressing the current aims, thanks to the METEOR multinational collaborative initiative. Furthermore, seventeen definitions of remission were analysed and compared, which is also unprecedented. The statistical methods used allowed us to analyse a large number of time points simultaneously, while adjusting for within-patient correlation. As data was collected from patients followed in regular clinics, there was a significate number of missing data. In order to account for possible selection bias, extensive sensitivity analyses were performed. In general, results were consistent across all the analyses. However, some limitations may also be considered, including the heterogeneity of the population, which may implicate genetic, social and demographic differences that might have influenced the results in a manner that we cannot estimate or account for. The remission criteria studied in this paper and even HAQ were developed mostly in Caucasian patients and their validity in such different populations was not clearly established yet. As patients were treated according to local standard of care, different

treatments could influence remission rates. We considered biologic treatment as the main possible treatment confounder, and adjustment for biologic treatment was included in the multivariable models, yielding similar results to the unadjusted models; however, the effect of other treatments was not analysed in this study.

Conclusions

In summary, the various remission definitions confirmed their association with physical function in a large prospective international clinical practice setting. In spite of this, importantly, many patients in non-remission have good functional status, while being in clinical remission does not equate to having good functional status. A multidimensional approach should be taken in order to help patients achieve this functional goal. Achievement of remission according to any of the indices may be more important than the selection of a specific one.

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Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to privacy policies but are available from the corresponding author on reasonable request.

Authors' contributions

PDC, JAPS and PMM designed the study. PDC and RJOF cleaned the database, which was provided by the Merit Foundation. PDC performed the statistical analyses under the supervision of PMM. PDC and PMM drafted the first version of the manuscript. All those listed as authors read, commented on, and approved the final manuscript.

Table 1. Summary of the clinical and demographic characteristics of the study population at first visit

Characteristics	All patients (total =32915)		Patients with full information on all definitions of remission (total =9902)	
		N1		N2
Female gender, n (%)	25470 (78.2)	32563	7962 (81.2)	9809
Age at visit, years (mean ± SD)	53.0 ± 14.8	32089	50.4 ± 14.0	9701
Disease duration, years (mean ± SD)	7.2 ± 8.4	25448	6.8 ± 7.9	8828
BMI, kg/m^2 (mean ± SD)	26.5 ± 5.2	13551	26.1 ± 5.3	4444
Smoker (current), n (%)	2700 (12.5)	21599	682 (8.3)	8182
RF positive, n (%)	19739 (73.3)	26924	7069 (77.4)	9137
ACPA positive, n (%)	11229 (70.3)	15981	3651 (74.3)	4916
Erosions, n (%)	8611 (53.7)	16027	2693 (55.9)	4820
Treatment with biological DMARDs, n (%)	3660 (11.1)	32915	889 (9.0)	9902
TJC28, n (mean ± SD)	8.6 ± 9.3	29908	11.2 ± 9.8	9902
SJC28, n (mean ± SD)	4.0 ± 5.1	30865	5.0 ± 5.5	9902
PGA, cm (mean ± SD)	4.6 ± 2.6	24764	5.2 ± 2.3	9902
PhGA, cm (mean ± SD)	4.1 ± 2.2	20406	4.3 ± 2.1	9902
HAQ (mean ± SD)	1.0 ± 0.8	12176	1.1 ± 0.8	3195

ACPA, anti-citrullinated peptide antibodies; BMI, Body Mass Index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DMARDs, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; MTX, methotrexate; N1 and N2, number of patients with information available; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; RF, Rheumatoid Factor; SD, standard-deviation; SJC28, 28-Swollen Joint Count; TJC28, 28-Tender Joint Count.

Table 2. Number (%) of visits in remission according to different definitions of remission*

Definition of remission		Number (%) of patients in remission at first METEOR visit	N1	Number (%) of visits in remission taking all visits into account	N2
ACR/EULAR Boolean-based		279 (1.9)	14696	2465 (4.5)	55261
SDAI ≤3.3		705 (6.1)	11562	7072 (17.1)	41420
CDAI ≤2.8		1188 (7.6)	15682	9579 (13.4)	71790
DAS-CRP<1.6	4v	2093 (16.0)	13067	19481 (38.6)	50517
	3v	2688 (15.5)	17352	23924 (39.1)	61214
DAS-ESR <1.6	4v	3699 (20.4)	18170	29256 (31.7)	92164
	3v	4238 (18.6)	22780	33774 (30.4)	111149
DAS28-CRP <2.6	4v	2326 (15.8)	14696	19252 (34.8)	55261
	3v	3097 (16.3)	19049	24742 (37.5)	65944
DAS28-ESR <2.6	4v	3295 (16.1)	20497	24895 (25.2)	98629
	3v	3765 (14.9)	25235	28647 (24.4)	117404
DAS28-CRP <1.9**	4v	1020 (6.9)	14696	9328 (16.9)	55261
	3v	1235 (6.5)	19049	11503 (17.4)	65944
DAS28-ESR <2.2**	4v	2032 (9.9)	20497	15922 (16.1)	98629
	3v	2032 (8.8)	25235	17875 (15.2)	117404
DAS28-CRP <2.4**	4v	1960 (13.3)	14696	16716 (30.2)	55261
	3v	2657 (13.9)	19049	21500 (32.5)	65944

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; N1 and N2, number of visits with information available; SDAI, Simplified Disease Activity Index. *Results at the first METEOR visit and taking all visits into account. **DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].

Table 3. Number and percentage of visits in good functional status (HAQ≤0.5) according to remission status

Definition of remission		Remission, at first METEOR visit		Remission, taking all visits into account	
		Yes	No	Yes	No
ACR/EULAR Boolean-based		182 (88.8)	1868 (29.3)	1556 (87.0)	10897 (34.1)
SDAI ≤3.3		403 (81.7)	827 (21.6)	4011 (78.1)	5005 (25.7)
CDAI ≤2.8		606 (80.5)	1364 (25.1)	4900 (78.5)	6775 (27.4)
DAS-CRP<1.6	4v	814 (58.6)	780 (20.5)	7826 (59.1)	3253 (19.3)
	3v	818 (54.5)	830 (21.1)	7836 (56.4)	3583 (20.7)
DAS-ESR <1.6	4v	1191 (60.8)	1211 (23.1)	9169 (63.2)	5105 (22.6)
	3v	1158 (56.7)	1314 (24.1)	8970 (60.4)	5693 (24.3)
DAS28-CRP <2.6	4v	1056 (64.6)	994 (20.1)	8316 (62.8)	4137 (20.2)
	3v	1091 (58.8)	1024 (20.5)	8512 (57.7)	4301 (21.3)
DAS28-ESR <2.6	4v	1154 (67.5)	1863 (25.8)	8292 (68.1)	7828 (26.5)
	3v	1067 (60.5)	2041 (27.0)	7711 (62.5)	8851 (28.7)
DAS28-CRP <1.9*	4v	567 (75.3)	1483 (25.4)	5002 (74.8)	7451 (27.6)
	3v	550 (68.2)	1565 (25.9)	4778 (65.8)	8035 (29.1)
DAS28-ESR <2.2*	4v	712 (69.3)	2305 (29.2)	5616 (72.3)	10504 (30.9)
	3v	611 (61.1)	2497 (30.1)	4921 (64.9)	11641 (32.7)
DAS28-CRP <2.4*	4v	941 (67.4)	1109 (21.4)	7583 (65.5)	4870 (22.0)
	3v	978 (61.2)	1137 (21.6)	7737 (60.2)	5076 (23.0)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI, Simplified Disease Activity Index. *DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)]. **Percentages presented in each column are independent (not complementary) of the next-side column.

Table 4. Longitudinal associations between good functional status (dependent variable) and remission (independent variable)*

Definition of remission		N	Univariable OR (95% CI) for HAQ≤0.5	N	Adjusted OR** (95% CI) for HAQ≤0.5
ACR/EULAR Boolean-based		33709	2.973 (2.730-3.236)	16247	2.555 (2.259-2.889)
SDAI ≤3.3		24633	3.774 (3.492-4.078)	12499	3.357 (3.012-3.742)
CDAI ≤2.8		30977	3.659 (3.417-3.920)	15137	3.152 (2.855-3.481)
DAS-CRP <1.6	4v	30097	3.086 (2.913-3.270)	15421	3.211 (2.935-3.513)
	3v	31186	2.740 (2.594-2.894)	15918	2.778 (2.555-3.022)
DAS-ESR <1.6	4v	37104	3.104 (2.950-3.266)	18520	2.956 (2.739-3.189)
	3v	38327	2.684 (2.557-2.817)	19066	2.630 (2.444-2.830)
DAS28-CRP <2.6	4v	33709	3.365 (3.185-3.554)	16247	3.292 (3.027-3.581)
	3v	34894	2.809 (2.670-2.956)	16751	2.803 (2.589-3.036)
DAS28-ESR <2.6	4v	41748	3.030 (2.886-3.182)	19577	2.838 (2.635-3.056)
	3v	43166	2.443 (2.332-2.559)	20162	2.338 (2.176-2.511)
DAS28-CRP <1.9***	4v	33709	3.050 (2.874-3.237)	16247	2.799 (2.571-3.048)
	3v	34894	2.400 (2.274-2.533)	16751	2.256 (2.089-2.436)
DAS28-ESR <2.2***	4v	41748	2.778 (2.630-2.933)	19577	2.486 (2.294-2.693)
	3v	43166	2.204 (2.090-2.326)	20162	1.989 (1.838-2.151)
DAS28-CRP <2.4***	4v	33709	3.296 (3.119-3.483)	16247	3.181 (2.925-3.459)
	3v	34894	2.740 (2.602-2.885)	16751	2.643 (2.443-2.860)

CDAI, Clinical Disease Activity Index; CI, Confidence Interval; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; N, number of visits with information available OR, Odds Ratio; SDAI, Simplified Disease Activity Index. *Results for the entire set of visits. **Adjusted OR for significant cofactors (age at visit, body mass index, female gender, rheumatoid factor positivity, presence of erosions, treatment with biologics). ***DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].

Table 5. Longitudinal associations between good functional status (dependent variable) and remission (independent variable)*

Definition of remission		OR (95% CI) for HAQ≤0.5; (n = 20808 visits; 5548 patients)	Adjusted OR** (95% CI) for HAQ≤0.5; (n =8 431 visits; 1799 patients)
ACR/EULAR Boolean-based		2.657 (2.395-2.947)	2.452 (2.087-2.881)
SDAI ≤3.3		3.629 (3.338-3.945)	3.549 (3.107-4.053)
CDAI ≤2.8		3.584 (3.297-3.896)	3.428 (3.007-3.908)
DAS-CRP <1.6	4v	3.396 (3.160-3.649)	3.793 (3.354-4.289)
	3v	3.016 (2.816-3.230)	3.342 (2.977-3.751)
DAS-ESR <1.6	4v	3.233 (3.015-3.467)	3.439 (3.062-3.862)
	3v	2.798 (2.615-2.994)	3.026 (2.706-3.383)
DAS28-CRP <2.6	4v	3.406 (3.173-3.657)	3.489 (3.102-3.925)
	3v	2.866 (2.680-3.065)	3.052 (2.729-3.413)
DAS28-ESR <2.6	4v	3.112 (2.893-3.348)	2.963 (2.636-3.331)
	3v	2.487 (2.323-2.663)	2.483 (2.217-2.781)
DAS28-CRP <1.9***	4v	2.938 (2.729-3.163)	2.966 (2.636-3.336)
	3v	2.276 (2.128-2.434)	2.371 (2.127-2.645)
DAS28-ESR <2.2***	4v	2.769 (2.560-2.995)	2.519 (2.223-2.855)
	3v	2.248 (2.082-2.427)	2.059 (1.823-2.324)
DAS28-CRP <2.4***	4v	3.311 (3.083-3.556)	3.368 (2.990-3.795)
	3v	2.704 (2.530-2.889)	2.815 (2.523-3.142)

CDAI, Clinical Disease Activity Index; CI, Confidence Interval; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; OR, Odds Ratio; SDAI, Simplified Disease Activity Index. Univariable OR and adjusted OR (with adjustment for significant cofactors) are both presented. *Results considering only visits with data for all definitions of remission. **Adjusted for: age at visit, body mass index, female gender, rheumatoid factor positivity, presence of erosions, treatment

with biologics. ***DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].

Figure 1. Flow chart representing the number of patients and visits taken into account in the analyses performed.
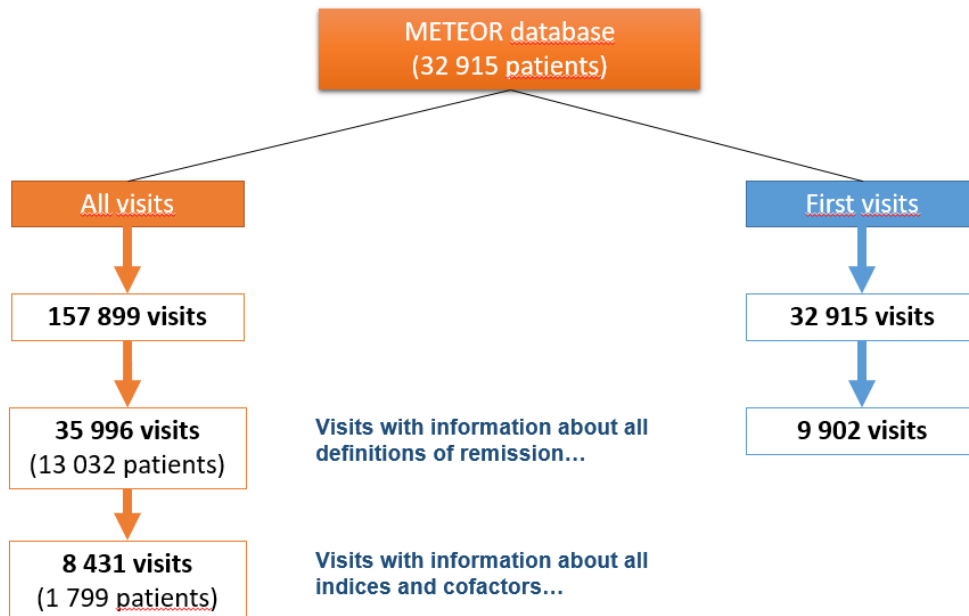
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Association of seventeen definitions of remission with functional status in a large international clinical practice cohort of patients with rheumatoid arthritis (METEOR cohort)

Supplementary table 1. Country of origin at first visit and taking all visits in account.

Country of origin	Number of patients at first visit (%)
India	10687 (32.5)
The Netherlands	7507 (22.8)
Portugal	4757 (14.5)
United Kingdom	1966 (6.0)
Mexico	1902 (5.8)
Ireland	1642 (5.0)
United States	1303 (4.0)
Other countries	3151 (9.3)
Total	32915 (100.0)

Supplementary table 2. Number and percentage of visits in remission according to different definitions of remission.*

Definition of remission		At first METEOR visit (Total =9902) n (%)	Taking all visits into account (Total =35996) n (%)
ACR/EULAR Boolean-based		92 (0.9)	1433 (4.0)
SDAI ≤3.3		508 (5.1)	6166 (17.1)
CDAI ≤2.8		503 (5.1)	6082 (16.9)
DAS-CRP-4v <1.6	4v	1405 (14.2)	14315 (39.8)
	3v	1463 (14.8)	14621 (40.6)
DAS-ESR-4v <1.6	4v	1224 (12.4)	12586 (35.0)
	3v	1254 (12.7)	12673 (35.2)
DAS28-CRP <2.6	4v	1156 (11.7)	12669 (35.2)
	3v	1303 (13.2)	13872 (38.5)
DAS28-ESR <2.6	4v	850 (8.6)	9287 (25.8)
	3v	899 (9.1)	9349 (26.0)
DAS28-CRP <1.9**	4v	482 (4.9)	6178 (17.2)
	3v	495 (5.0)	6483 (18.0)
DAS28-ESR <2.2**	4v	534 (5.4)	5962 (16.6)
	3v	545 (5.5)	5836 (16.2)
DAS28-CRP <2.4**	4v	977 (9.9)	11059 (30.7)
	3v	1103 (11.1)	12055 (33.5)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI, Simplified Disease Activity Index; vs, versus. *Considering only visits with information on all definitions of remission. **DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].

Supplementary table 3. Visits with good functional status (HAQ≤0.5) according to remission status in different definitions.*

Definition of remission		Remission, at first METEOR visit		Remission, taking all visits into account	
		Yes	No	Yes	No
ACR/EULAR Boolean-based		48 (87.3)	840 (26.8)	911 (86.8)	6733 (34.1)
SDAI ≤3.3		277 (81.7)	611 (21.4)	3498 (77.6)	4146 (25.4)
CDAI ≤2.8		266 (81.3)	622 (21.7)	3428 (77.8)	4216 (25.7)
DAS-CRP <1.6	4v	508 (56.8)	380 (16.5)	5748 (58.6)	1896 (17.2)
	3v	500 (53.8)	388 (17.1)	5602 (56.4)	2042 (18.8)
DAS-ESR <1.6	4v	452 (58.2)	436 (18.0)	5247 (61.5)	2397 (19.5)
	3v	437 (55.1)	451 (18.8)	5037 (58.9)	2607 (21.3)
DAS28-CRP <2.6	4v	467 (62.9)	421 (17.2)	5379 (61.7)	2265 (18.7)
	3v	470 (56.5)	418 (17.7)	5367 (56.8)	2277 (20.0)
DAS28-ESR <2.6	4v	353 (67.4)	535 (20.0)	4240 (67.2)	3404 (23.5)
	3v	326 (58.7)	562 (21.3)	3843 (61.4)	3801 (26.1)
DAS28-CRP <1.9**	4v	241 (77.0)	647 (22.4)	3268 (73.7)	4376 (26.7)
	3v	206 (65.2)	682 (23.7)	2984 (64.2)	4660 (28.8)
DAS28-ESR <2.2**	4v	224 (68.7)	664 (24.1)	2926 (71.9)	4718 (28.2)
	3v	202 (61.4)	686 (23.9)	2494 (64.4)	5150 (30.4)
DAS28-CRP <2.4**	4v	419 (66.0)	469 (18.3)	4934 (64.4)	2710 (20.6)
	3v	414 (58.5)	474 (19.1)	4876 (59.0)	2768 (22.1)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI, Simplified Disease Activity Index; vs, versus. *Considering only visits with data on all definitions of remission DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)]. **Percentages presented in each column are independent (not complementary) of the next-side column.